

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A61K 31/57 // (A61K 31/57, 31:165)</p>		A1	<p>(11) International Publication Number: WO 99/64014 (43) International Publication Date: 16 December 1999 (16.12.99)</p>		
<p>(21) International Application Number: PCT/SE99/01031</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p>			
<p>(22) International Filing Date: 10 June 1999 (10.06.99)</p>		<p>(30) Priority Data: 9802073-8 11 June 1998 (11.06.98) SE</p>			
<p>(71) Applicant (<i>for all designated States except US</i>): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).</p>		<p>(72) Inventor; and (75) Inventor/Applicant (<i>for US only</i>): EKSTRÖM, Tommy [SE/SE]; Astra Draco AB, P.O. Box 34, S-221 00 Lund (SE).</p>			
<p>(74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).</p>		<p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>			
<p>(54) Title: USE OF A COMPOSITION COMPRISING FORMOTEROL AND BUDESONIDE FOR THE PREVENTION OR TREATMENT OF AN ACUTE CONDITION OF ASTHMA</p>					
<p>(57) Abstract</p> <p>The present invention relates to use of a composition for symptomatic relief, when needed, comprising, in admixture (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and (b) a second active ingredient which is budesonide; for the manufacture of a medicament for use in the prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma. The invention further relates to a method for prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma by administering, by inhalation, a composition comprising the first and second active ingredients as defined previously.</p>					

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AI	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

USE OF A COMPOSITION COMPRISING FORMOTEROL AND BUDESONIDE FOR THE PREVENTION OR TREATMENT OF AN ACUTE CONDITION OF ASTHMA**FIELD OF THE INVENTION**

- 5 The present invention relates to use of a composition for symptomatic relief, when needed, comprising, in admixture
 - (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and
 - (b) a second active ingredient which is budesonide;
- 10 for the manufacture of a medicament for use in the prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma. The invention further relates to a method for prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma by administering, by inhalation, a composition comprising the first and second active ingredients as defined previously.
- 15

BACKGROUND OF THE INVENTION

Despite recent advances in the awareness of asthma and the introduction of powerful and effective anti-asthma drugs, asthma remains a poorly understood and frequently poorly treated disease. There have been recent advances in the treatment of the disease which result from the recognition that asthma is a chronic inflammatory disease. Therapy is now aimed at both controlling the symptoms and reducing the inflammation. The symptoms may be controlled by β_2 -adrenoceptor agonists such as terbutaline, salbutamol, formoterol and salmeterol. Prophylactic therapy is typically provided by steroids such as beclomethasone dipropionate, fluticasone propionate, mometasone furoate and budesonide.

In spite of modern maintenance treatment too many asthmatic patients are undertreated for a number of reasons with a negative impact on their quality of life. Too complicated therapy with different medications and devices may lead to misunderstanding and commu-

nication problems between patient and doctor. Poor compliance is a common phenomenon. Improved patient education may partly counteract this, but does not completely solve the problem. A new and more simple approach to asthma treatment could thus be of tremendous help for many patients suffering from respiratory disease, particularly asthma. The 5 combination of budesonide and formoterol in the same device as suggested in PCT applications WO 93/11773 and WO 98/15280 (both to Astra AB of Sweden) offers a favorable pathway to improve today's asthma management with an excellent safety profile. However, although having an adequate regular, e.g. bid. treatment with such a combination, many patients will now and then run into acute situations with a higher frequency and 10 severity of exacerbations, when additional medication is needed. Such an additional medication is often a β_2 -adrenoceptor agonist with fast onset, normally terbutaline or salbutamol. A second medicament is thus needed, and this can negatively affect the overall compliance of the patient. There is thus need for a neat way of handling maintenance treatment together with the treatment of acute situations which .

15

SUMMARY OF THE INVENTION

It is an object of the present invention to provide use of a suitable composition for the manufacture of a medicament for the treatment of acute episodes of asthma as a 20 complement to maintenance treatment.

More specifically, according to the invention there is provided use of a composition for symptomatic relief when needed comprising, in admixture
(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt 25 or solvate thereof or a solvate of such a salt; and
(b) a second active ingredient which is budesonide;
for the manufacture of a medicament for use in the prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma.

Use of the present composition, when needed, relates to use of said composition during one or more of the following conditions:

- i) an acute condition of asthma, i.e. acute asthma attacks,
- ii) intermittent asthma and/or
- 5 iii) short periods (episodes) of acute attacks of bronchospasms in chronic asthma.

Acute asthma attacks may occur on an irregular basis when exposed to an agent e.g. during the pollen season, a virus infection, cold air, perfumes or any other agent(s) triggering an asthma attack in the patient.

10 It lies within the scope of the present invention, to use the compositions comprising active compounds (a) and (b) for treating acute conditions of asthma, intermittent asthma and episodes in chronic asthma, in addition to treating chronic asthma on a regular basis, with the same active compounds (a) and (b) or one or more different active compounds, 15 preferably selected from short-acting β -agonists, long-acting β -agonists and glucocorticosteroids.

We contemplate preventive use when the patient expects to encounter asthma inducing conditions e.g. intends to take exercise or go into smoky conditions.

20 According to a further aspect of the invention a method of prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma, when needed, which comprises administering, by inhalation, to a patient an effective amount of a composition comprising, in admixture:
25 (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and
(b) a second active ingredient which is budesonide.

30 According to the present invention it has surprisingly been found that the medicament can be administered when needed to a patient with an acute attack of asthma.

The recommended dose regimen described in the prior art as disclosed above is twice a day. This dose recommendation was a result of a concern not to have too high an administration of the active compounds. However, in the present invention it has been found that 5 it is possible for the patient to administer this mixture as often as needed.

The combination of formoterol and budesonide can be used as a rescue medication. Worsening of symptoms can be counteracted by incremental use of the combination for symptom relief, e.g. during exacerbations with the additional steroid component coming in 10 as early as possible to suppress the enhanced airway inflammation. The long duration of formoterol will reduce the risk of too frequent dosing. When taking the combination budesonide/formoterol when needed the severity of exacerbations can be reduced. The as needed use (Pro Re Nata, PRN) will also minimize the difficulty of predicting which 15 patients will be controlled on a low dose of inhaled steroid rather than increasing the steroid dose before adding a long-acting β_2 -agonist. Under-treatment with inhaled glucocorticosteroids following a too low maintenance dose will be more or less "self-corrected" by the rescue usage according to the present invention. The PRN use of the combination will always give some beneficial anti-inflammatory effects even if it is used by the patient only for rescue purposes. A treatment for patients suffering from respiratory 20 disease, particularly asthma (including allergic conditions, e.g. episodic or intermittent asthma), will therefore be to use the combination formoterol/budesonide for maintenance therapy as well as on an as needed basis (for rescue purposes), e.g. for prevention of exercise and/or allergen induced asthma.

DETAILED DESCRIPTION OF THE INVENTION

Formoterol is a compound which can exist in several stereochemical forms. The present invention includes the individual stereoisomers as well as mixtures thereof. It is intended that the present invention includes geometrical isomers, rotational isomers, racemates, diastereomers and enantiomers, in particular the R,R enantiomer of formoterol.

Suitable physiologically salts of formoterol include acid addition salts derived from inorganic and organic acids such as the hydrochloride, hydrobromide, sulfate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, salicylate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxy-naphthalene-carboxylate or oleate. Formoterol is preferably used in the form of its fumarate salt and as a dihydrate of this salt.

15

The present invention also encompasses compositions comprising the 22R epimer of budesonide as the second active ingredient.

A suitable unit dose of formoterol (as fumarate dihydrate) is in the range of from 1 μ g to 48 μ g, preferably from 2 μ g to 24 μ g, and more preferably between 3 μ g and 12 μ g. The daily dose of formoterol (as fumarate dihydrate), including maintenance therapy, should be in the range of from 1 μ g to 100 μ g, preferably from 2 μ g to 60 μ g, and more preferably from 3 μ g to 48 μ g.

25 A suitable unit dose of budesonide is in the range of from 20 μ g to 1600 μ g, suitably from 30 μ g to 800 μ g, preferably from 50 μ g to 400 μ g, and more preferably between 100 μ g and 200 μ g. The daily dose of budesonide, including maintenance therapy, should be in the range of 20 μ g to 4800 μ g, preferably from 30 μ g to 3200 μ g, and more preferably from 40 μ g to 1600 μ g. The particular dose regimen will depend on the patient (age, sex, weight etc.) and the severity of the disease (mild, moderate, severe asthma etc.).

The molar ratio of the first active ingredient (as formoterol) to the second active ingredient of the invention, suitably lies in the range of from 1:1 to 1:100, preferably from 1:1 to 1:70, and more preferably from 1:1 to 1:50.

5

Preferably the mixture comprises one or more pharmaceutically acceptable additives, diluents or carriers, more preferably in an amount of, from 50 µg to 4000 µg in each dose, most preferably in an amount of from 100 µg to 2000 µg and most preferably from 100 µg to 1000 µg. Examples of suitable additives, diluents or carriers include lactose, dextran, 10 manitol or glucose. Preferably lactose is used, and more preferably as the monohydrate.

10

One or more of the ingredients of the mixture may be in the form of dry powder, more preferably a small particle dry powder, most preferably an agglomerated small particle dry powder. Alternatively one or more of the active ingredients (a) or (b) are in the form of an 15 ordered mixture with diluent, additive or carrier. The ingredients used in the invention can be obtained in these preferred forms using methods known to those skilled in the art. The particle size of the active ingredients is preferably less than 10 µm.

15

Administration may be by inhalation orally or intranasally. The ingredients of the system 20 are preferably adapted to be administered from a dry powder inhaler, a pressurized metered dose inhaler, or a nebulizer.

25

When the ingredients of the system are adapted to be administered from a pressurized inhaler, they are preferably in a small particle form. They are dissolved, or, preferably, suspended in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluorocarbons. Especially preferred propellants are P134a (tetrafluoroethane), P152a (difluoroethane) and P227 (heptafluoropropane) each of which may be used alone or in combination. They are optionally used in combination with one or more other propellants and/or one or more surfactants and/or one or more other excipients, for example ethanol, a lubricant, an antioxidant and/or a stabilizing agent.

30

When the ingredients of the system of the invention are adapted to be administered via a nebulizer they may be in the form of a nebulized aqueous suspension or solution, with or without suitable pH or tonicity adjustment, either as a unit dose or multidose formulation.

5

EXAMPLES

The ingredients can be formulated as illustrated by the following examples which are not intended to limit the scope of the invention.

10

In the examples micronization is carried out in a conventional manner such that the particle size range for each component is suitable for administration by inhalation. Turbuhaler³ is a trademark of Astra AB.

15

EXAMPLE 1

4.5 Parts by weight of formoterol fumarate dihydrate were mixed with 915 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 80 Parts by weight of micronized budesonide were added to the conditioned product by mixing and homogenizing with a low pressure jet mill. The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler.³

EXAMPLE 2

25

9 Parts by weight of formoterol fumarate dihydrate were mixed with 831 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 160 Parts by weight of micronized budesonide were added to the conditioned product by mixing and homogenizing with a low

pressure jet mill. The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler.⁹

EXAMPLE 3

5

6 Parts by weight of formoterol fumarate dihydrate were mixed with 894 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 100 Parts by weight of micronized budesonide were added to the conditioned product by mixing and homogenizing with a low 10 pressure jet mill. The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler.⁹

EXAMPLE 4

15

12 Parts by weight of formoterol fumarate dihydrate were mixed with 788 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 200 Parts by weight of micronized budesonide were added to the conditioned product by mixing and homogenizing with a low pressure jet mill. The mixture was then spheronized using the process of EP-A-721 331 20 and filled into the storage compartment of Turbuhaler.⁹

EXAMPLE 5

25

A patient on maintenance treatment with the fixed combination formoterol fumarate dihydrate/budesonide in a dose of 4.5/80 µg or 4.5/160 µg bid additionally uses the same combination either for rescue purposes once or twice daily to treat sporadic breakthrough symptoms, or as needed to treat exacerbations during one or two weeks, with a maximum daily dose of 36/640 µg (8 puffs of 4.5/80 µg) and 36/1280 µg (8 puffs of 4.5/160 µg), respectively.

30

EXAMPLE 6

A patient with intermittent asthma uses the fixed combination formoterol fumarate dihydrate/budesonide as sole medication to be taken as needed until the asthma resolves.

- 5 The highest recommended daily dose will be either 36/640 µg (8 puffs of 4.5/80 µg) or 36/1280 µg (8 puffs of 4.5/160 µg) for a period not exceeding 8-120 weeks. If symptoms still persist after that period of time - regular maintenance therapy should be considered.

CLAIMS

1. Use of a composition for symptomatic relief, when needed, comprising, in admixture

5 (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and
(b) a second active ingredient which is budesonide;

for the manufacture of a medicament for use in the prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma.

10

2. Use according to claim 1, wherein the molar ratio of (a) to (b) calculated as formoterol to budesonide is from 1:1 to 1:100, preferably from 1:1 to 1:70.

15

3. Use according to claim 1 or 2, wherein the first active ingredient is formoterol fumarate dihydrate.

4. Use according to any previous claim, wherein the first active ingredient is the R,R enantiomer of formoterol.

20

5. Use according to any previous claim, wherein a unit dose of formoterol lies in the range of from 1 μ g to 48 μ g, preferably between 3 μ g to 12 μ g, calculated as formoterol fumarate dihydrate.

25

6. Use according to any previous claim, wherein the daily dose of formoterol, including maintenance therapy, lies in the range of from 1 μ g to 100 μ g, preferably from 2 μ g to 60 μ g, calculated as formoterol fumarate dihydrate.

30

7. Use according to any previous claim, wherein the second active ingredient is the 22R epimer of budesonide.

8. Use according to any previous claim, wherein a unit dose of budesonide lies in the range of from 20 µg to 1600 µg, preferably between 50 µg to 400 µg.

9. Use according to any previous claim, wherein the daily dose of budesonide, including maintenance therapy, lies in the range of from 20 µg to 4800 µg, preferably from 30 µg to 3200 µg.

10. Use according to any previous claim, wherein the particle size of the active ingredients (a) and (b) is less than 10 µm.

11. Use according to any previous claim, wherein the composition additionally comprises one or more pharmaceutically acceptable additives, diluents or carriers.

12. Use according to claim 11, wherein the pharmaceutically acceptable additive, diluent or carrier is lactose monohydrate.

13. A method of prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma, when needed, which comprises administering, by inhalation, to a patient an effective amount of a composition comprising, in admixture:

- (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and
- (b) a second active ingredient which is budesonide.

25 14. The method according to claim 13, wherein the molar ratio of (a) to (b) calculated as formoterol to budesonide is from 1:1 to 1:100, preferably from 1:1 to 1:70.

15. The method according to claim 13 or 14, wherein the first active ingredient is formoterol fumarate dihydrate.

16. The method according to any of claims 13 to 15, previous claim, wherein the first active ingredient is the R,R enantiomer of formoterol.

17. The method according to any of claims 13 to 16, wherein a unit dose of formoterol lies in the range of from 1 μ g to 48 μ g, preferably between 3 μ g to 12 μ g, calculated as formoterol fumarate dihydrate.

18. The method according to any of claims 13 to 17, wherein the daily dose of formoterol, including maintenance therapy, lies in the range of from 1 μ g to 100 μ g, preferably from 2 μ g to 60 μ g, calculated as formoterol fumarate dihydrate.

19. The method according to any of claims 13 to 18, wherein the second active ingredient is the 22R epimer of budesonide.

20. The method according to any of claims 13 to 19, wherein a unit dose of budesonide lies in the range of from 20 μ g to 1600 μ g, preferably between 50 μ g to 400 μ g.

21. The method according to any of claims 13 to 20, wherein the daily dose of budesonide, including maintenance therapy, lies in the range of from 20 μ g to 4800 μ g, preferably from 30 μ g to 3200 μ g.

22. The method according to any of claims 13 to 21, wherein the particle size of the active ingredients (a) and (b) is less than 10 μ m.

23. The method according to any of claims 13 to 22, wherein the composition additionally comprises one or more pharmaceutically acceptable additives, diluents or carriers.

24. The method according to claim 23, wherein the pharmaceutically acceptable additive, diluent or carrier is lactose monohydrate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01031

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/57 // (A61K 31/57, 31:165)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9311773 A1 (AKTIEBOLAGET ASTRA), 24 June 1993 (24.06.93), See page 1409 - page 1410 --	1-24
X	The New England Journal of Medicine, Volume 337, No 20, November 1997, Romain A. Pauwels et al, "Effect of Inhaled Formoterol and Budesonide on Exacerbations of Asthma" page 1405 - page 1411 -- -----	1-24

<input type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> See patent family annex.
* Special categories of cited documents:		
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
"E" earlier document but published on or after the international filing date	"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search	Date of mailing of the international search report	
20 Sept 1999	11 -10- 1999	
Name and mailing address of the ISA / Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Anna Sjölund/Els Telephone No. + 46 8 782 25 00	

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/SE99/01031**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **13-24**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/01031

Claims 13-24 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

30/08/99

PCT/SE 99/01031

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9311773 A1	24/06/93	AU 673660 B	21/11/96
		AU 3085892 A	19/07/93
		CA 2123909 A	24/06/93
		CZ 9401434 A	15/12/94
		EP 0613371 A	07/09/94
		HR 921445 A	31/12/94
		HU 75156 A	28/04/97
		HU 9401843 D	00/00/00
		JP 7502036 T	02/03/95
		NO 942116 A	07/06/94
		NZ 246050 A	21/12/95
		SG 48301 A	17/04/98
		SK 73394 A	08/03/95
		US 5674860 A	07/10/97